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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,182	06/19/2002	William A. Banks	01017/36667	7965

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EXAMINER

KOLKER, DANIEL E

ART UNIT	PAPER NUMBER
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1649

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/03/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/049,182

Applicant(s)

BANKS, WILLIAM A.

Examiner

Daniel Kolker

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 January 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-76 is/are pending in the application.
- 4a) Of the above claim(s) 6-76 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 1-76 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application
- ☐ Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on 18 December 2006 and 16 January 2007 have been entered.
2. Claim 77 is canceled; claims 1 – 76 are pending.

Election/Restrictions

3. Claims 6 – 76 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 1 March 2005.
4. Claims 1 – 5 are under examination.

Withdrawn Rejections and Objections

5. The following rejections and objections set forth in the previous office action are withdrawn:

A. The rejections under 35 USC 112 are withdrawn in light of the amendments. The claims are no longer drawn to fragments generically, but rather to certain very specific fragments and variants recited in the claims.

Maintained Rejections and Objections

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1 – 5 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Banks (1996, of record), in view of Borges (1994, of record) and Caro (1996, of record).

This rejection is maintained for the reasons of record. Briefly, Banks teaches that leptin enters the brain via a saturable transporter, Borges teaches that epinephrine modulates the exclusionary properties of the blood-brain barrier (BBB), and Caro provides motivation to increase the amount of leptin entering the brain. For the sake of brevity the examiner's logic will not be repeated here, rather applicant is referred to the previous office actions. Instead, the examiner will only address applicant's arguments that the claimed invention would not have been obvious to one of ordinary skill in the art.

Applicant argues, on pp. 15 – 17 that the rejection under 35 USC 103 should be withdrawn because:

a) there is no suggestion that epinephrine, which is a non-specific disrupter of the BBB, would act in a specific manner to modulate the leptin transporter, as applicant has discovered;

b) the post-filing reference by Banks (Banks C6, cited on IDS) disclosed that transport of TNF-alpha, which is similar in size to leptin, is not increased by epinephrine, suggesting a lack of expectation of success;

c) the declaration submitted by Dr. Banks indicates that phenylephrine is not effective in increasing specific transport of leptin; and

d) the post-filing reference by Nonoka (exhibit A submitted with the response) indicates that LPS, which disrupts the BBB inhibits transport of leptin across the BBB.

Applicant's arguments have been fully considered but they are not persuasive. Each of the four points listed above will be addressed in turn.

With respect to a), the examiner believes this is not germane to the claims under examination. Of course the claims require that the administration of leptin "is effective to modulate the transport of leptin across the blood brain barrier through the specific leptin transporter". However, this will necessarily happen once the appropriate dose of epinephrine is administered. As set forth in the office actions mailed previously, the reference by Borges indicates 100 nM of epinephrine modulates the permeability of the BBB. This is one of the doses now discovered by applicant to specifically modulate the leptin transporter, however before applicant had discovered this the same dose was known to be effective in increasing the permeability of the BBB. Thus while there is not an indication in Borges that the dose of epinephrine would specifically act on the leptin transporter, the prior art provides motivation to

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select this dose to increase the permeability of the BBB to those agents which are normally excluded. Of course Banks (1996) teaches that leptin is usually excluded, and Caro provides the motivation to increase the transport of leptin through the BBB, as Caro teaches that the exclusion of leptin from the brain may be a cause of obesity, and that in order to treat obesity the amount of leptin reaching the hypothalamus should be increased. Therefore the prior art references, taken together, describe the problem (not enough leptin reaching the brain leads to obesity), the mechanism underlying the problem (leptin is excluded from the brain by its BBB transporter) and the solution to the problem (increase BBB permeability by administering epinephrine at 100 nM). Note that an examiner's conclusion of whether an invention would have been obvious can have a different motivation than applicant's reason for performing the invention.

With respect to b), whether or not TNF-alpha BBB transport by its specific receptor is modulated by administration of epinephrine is not on point. First, it is important to note that the reference by Banks referred to on p. 16 of the remarks was published two years after the earliest effective filing date of this application. So the reference could not possibly speak to the non-obviousness of the invention, at the time it was made, since the reference was not available to the artisan of ordinary skill at the time the invention was made. Second, even if the reference had been available at the time the invention was made, it still would not constitute a teaching away. The reference does not report that the amount of TNF-alpha in the brain is not changed after epinephrine administration, but rather it reports that the amount of TNF-alpha specifically transported by the TNF transporter is not changed. Furthermore, it is important to note that the reference by Caro does not suggest that TNF-alpha transport should be increased, but rather that leptin transport should be increased.

With respect to c), the declaration under 37 CFR 1.132 filed 18 December 2006 is insufficient to overcome the rejection of claims 1 – 5 based upon obviousness as set forth in the last Office action because: it does not speak to the non-obviousness of the invention claimed. The declaration provides evidence that phenylephrine is not effective in modulating the specific leptin transporter of the BBB. This speaks to non-enablement of a claim to modulation of transport of leptin through its specific BBB transporter by a generic adrenergic agonist, but no claims under examination are drawn to modulation by adrenergic agonists generically. Furthermore, the declaration does not provide any evidence that the invention now claimed would not have been obvious over the references of record. While paragraph 3 of the

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declaration indicates that certain mechanistic findings as to how epinephrine actually increases the amount of leptin that crosses the BBB were made in the declarant's laboratory, such a finding is not claimed; what is claimed is a method of modulating leptin transport by administering epinephrine. As stated above and in previous office actions, the prior art of record provides very strong guidance to select a specific dose of epinephrine that applicant has now found modulates leptin transport through a certain mechanism. Nothing in the declaration indicates that the invention would not have been obvious to one of ordinary skill in the art, as the art specifically guides the artisan to select the appropriate dose of epinephrine to increase the amount of leptin that enters the brain from the circulation.

With respect to d), the arguments are quite similar to b) above. Applicant has cited a reference, which is not prior art, which does not teach away from the non-obviousness of the invention. The reference by Nonaka teaches that LPS, which disrupts the BBB, decreases the transport of leptin across the BBB. Applicant appears to argue that the decrease in leptin transport is inconsistent with an increase induced by epinephrine, thereby making the invention non-obviousness. The claims, however, are not limited to methods of increasing transport from blood to brain, but rather are drawn to modulating (i.e. either increasing or decreasing) transport across the BBB. Nevertheless, no claims are drawn to methods of administering LPS. Rather, the claims are drawn to methods of administering epinephrine, which is structurally distinct from LPS. Furthermore, even if the reference by Nonaka had been on point to the non-obviousness of the claimed invention, which it is not, it still would not have been available to the artisan of ordinary skill at the time the invention was made, and therefore could not have been considered by the artisan. Because the reference was published five years after the earliest effective filing date and fails to teach away from the obvious nature of the claimed invention, the argument that the findings set forth in Nonaka teach away from the invention are not persuasive.

New Rejections

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Claim 5 recites the limitation "the adrenergic agonist" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Daniel E. Kolker, Ph.D.

March 27, 2007



ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER